Role of Coagulation Factors in Diabetic Retinopathy

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ABSTRACT

The role of coagulation factors in diabetic retinopathy was studied in non-insulin-dependent diabetic patients. Patients with retionopathy had higher levels of beta thromboglobulin, von Willebrand factor and fibrinogen levels compared to diabetics without retinopathy and controls. Serum magnesium levels were not significantly different between the groups studied. The role of coagulation factors in the aetiopathogenesis of diabetes retinopathy merits further study.

The factors implicated in diabetic microangiopathy include changes in physical and functional properties of red blood cells, alterations in platelet aggregation and adhesiveness, prostaglandin metabolism and changes in clotting factors and blood viscosity [1]. Some of these changes may precede the development of retinopathy and may be related to the severity of the disease.

In this study, some of the important biochemical parameters in blood which give an indication of the changes occurring in coagulation processes were studied in patients with non-insulin-dependent diabetes mellitus (NIDDM). Three groups of diabetic patients were studied: NIDDM without retinopathy, NIDDM with background diabetic retinopathy and NIDDM with proliferative diabetic retinopathy. The aim of the study was to look for possible differences in coagulation factors between these three groups of patients.

METHODS

The diabetic patients selected for the study satisfied the following criteria:

1. Diagnosis of NIDDM was established as per the WHO study group report [2].
2. All patients were on oral hypoglycaemic agents for at least 2 years from the date of diagnosis of the disease.
3. Fundus examination was carried out in detail both by direct ophthalmoscopy.
4. The grading of retinopathy was done according to the Hammersmith Hospital grading system [3].

Sixty-two consecutive patients satisfying the above criteria were recruited for the study. The healthy volunteers from the staff of the centre were also studied as control subjects. None of the control subjects had diabetes nor a family history of diabetes. All the study subjects (diabetics and controls) had normal haemograms, liver function tests and kidney function tests. It was ensured that none of the study subjects were on exogenous hormone administration as blood factors are known to be affected by hormones.

Blood Collection

Plasma samples were collected in the fasting state for glucose, glycosylated haemoglobin (HbA_1) , fibrinogen, beta thromboglobulin (BTG), von Willebrand factor (vWF) and C- Reactive Protein (CRP) estimations. For magnesium, serum samples were used. Plasma was collected in EDTA for glucose and HbA_1 and in citrate for other parameters. Post-prandial glucose was also measured. Glucose and HbA_1 assays were done on the same day and glucose was estimated by the glucose oxidase method using Boehringer Mannheim (Germany) reagents on Hitachi 704 autoanalyser. HbA_1 was measured by the colorimetric procedure of Eross et al[4]. Magnesium and fibrinogen were measured by the xylidyl blue and batroxobin procedures respectively by an auto analyser. Elisa procedures were used for vWF and BTG estimations (Boehringer Mannheim kits, Germany).

Statistical comparisons were done using the wilcoxon rank square test.

RESULTS

Table 1 shows the results in the three diabetic groups in comparison with the control group. There was no statistical difference between the mean ages of the study groups. The duration of diabetes was greater in the patients with retinopathy, but the differences were not statistically significant. The fasting and post-prandial plasma glucose and HbA_1 values were also similar in the three groups of diabetic patients.

Table 2 shows the levels of the coagulation factors in the different study groups. Serum fibrinogen values were higher in the diabetic patients with retinopathy (Group 3& 4) . Moreover the levels were higher in (Group 4) patients with proliferative diabetic retinopathy. In patients without retinopathy the mean value was similar to that in the control group.

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Table 1

Clinical and Biochemical Parameters in the Patient Groups and Controls

	Group 1 Control	Group 2 without DR	Group 3 BDR	Group 4 PDR
No. of Patients	10	18	24	20
Male : Female	6 : 4	8 : 10	17 : 7	16 : 4
Age (years)	57±7	53±13	56±9	56±8
Duration of Diabetes (years)	--	9.6±5.5	11.4±6.3	13.2±6.8
FPG (mg/dl)	98±8	184 ± 89	187±67	176±52
PPG (mg/dl)	135±5	240±76	280±96	245±78
HbA_1 (%)	7.0±0.6	9.2±0.5	9.6±0.7	9.6 ± 0.6

Without DR = Without Retinopathy
BDR = Background Diabetic Retinopathy
PDR = Proliferative Diabetic Retinopathy
FPG = Fasting Plasma Glucose
PPG = Post-prandial Plasma Glusose
HBA_1 = Glycosylated Haemoglobin

BTG concentrations were significantly higher in all groups of diabetic patients and again the highest values were seen in patients with proliferative retinopathy.

Table 2

Coagulation Factors in the Study Groups

	Group 1 Control	Group 2 withoutDR	Group 3 BDR	Group4 PDR
Fibrinogen	282±44	287±100	297±78	366±94 a,b,c
BTG (mg/dl)	28±8	72±56[a]	86±62[a]	118±56
Mg (mg/dl)	1.5±0.6	1.6±0.5	1.6±0.7	1.6±0.7
vWF (%)	72±31	84±20	113±36[a]	93±28[b]
CRP Positive	Nil	3/18 (16.7%)	8/24 (33.3%)	7/20 (35%)

a = P < p.001 for all vs. controls
b = P < 0.001 Group 2 vs. Group 4
c = P < 0.05 Group 3 vs Group 4
FPG = Fasting Plasma Glucose
PPG = Post-prandial Plasma Glucose
HBA_1 = Glycosylated Haemoglobin
BTG = Beta Thromboglobulin
Mg = Magnesium
VWF = von Willebrand factor
CRP = C- Reactive Protein
Without DR = Without Retinopathy
BDR = Background Diabetic Retinopathy
PDR = Proliferative Diabetic Retinopathy

Serum magnesium levels were not significantly different between the three diabetic groups compared to the control group.

Significantly higher values of vWF were noted in the groups with retinopathy (Group 3 and 4), but diabetics without retinopathy (Group 2) showed no difference from the control group.

None of the control subjects showed detectable concentrations of CRP, but many of the diabetic patients showed increased concentrations and the number of positive cases were higher in the Groups 3 & 4 i.e. patients with retinopathy.

DISCUSSION

Despite similar plasma glucose and HbA_1 values, differences in concentrations of coagulation and platelet factors were observed in diabetic patients with and without retinopathy. CRP and fibrinogen, which are involved in coagulation and plasma viscosity regulation were increased in patients with mild to severe retinopathy. As the concentration of fibrinogen rises, it causes increased blood viscosity and the blood flow to the retina decreases leading to deposition of platelets and fibrin with subsequent thrombus formation [1]. Direct association of elevated fibrinogen concentration with severity of retinopathy was observed in our patients.

vWF, synthesized in the endothelial cell, promotes the aggregation and adhesion of the platelets, both the processes being recognized as causative factors for microvascular pathology [5,6]. In patients without retinopathy, there was no increase in vWF concentration; but the values were significantly higher in patients with retinopathy. Increased values were also observed by other groups of workers [7,8] but contrary to the finding in this study, increased values have been noted even in diabetic patients without diabetic retinopathy by some workers [1].

It is unlikely that vWF levels play a primary role in the pathogenesis of diabetic retinopathy. Ho et al [9] have reported on a patient with established Von Willebrand's disease, who developed proliferative diabetic retinopathy despite markedly subnormal Von Willebrand factor levels.

Increased platelet turnover is indicated by greater leakage of BTG into plasma [1]. In our study, we found high BTG levels in diabetics with retinopathy and highest levels in those with proliferative diabetic retinopathy (PDR). This supports the observations of earlier workers [10 – 11].

Low concentrations of serum magnesium have been implicated in the causation of retinopathy by some workers [1]. We were unable too confirm this finding. The reason for this observation is unclear, although it is possible that treatment with mineral and vitamin supplements may have altered the blood chemistry in some of these patients.

It may be concluded that while blood coagulation factors may not be the most important risk factors for the development of retinopathy in NIDDM patients, they may atleast play a secondary role in the aetiopathogensis of diabetic retinopathy. This merits longitudinal studies on diabetic retinopathy at different stages of its natural history to further delineate the role of coagulation factors in aetiopathogensis of diabetic retinopathy.

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